REMARKS

Favorable reconsideration is respectfully solicited in view of the following remarks.

Initially, Applicant wishes to express its sincere thanks for the courtesy and cooperation provided to its representatives by Examiner Donna Jagoe during the personal interview held on February 16, 2010. The following is a summary of the items discussed during the interview.

Claims 19-40 have been cancelled without prejudice to the filing of a divisional application thereto.

Claims 41, 61 and 62 have been amended to make minor corrections as discussed during the interview.

Claims 42-45, 47-48, 51 and 54 have been amended in minor respects to reorganize the claimed subject matter and change the dependencies.

Claim 63 is cancelled without prejudice.

New claims 64-68 are added for additional patent protection and are supported in the specification at page 8, lines 19-26; page 12, lines 8-28, Table 1 on page 15; and Table 2 on page 17 of the specification. Note that sodium tetraborate is also known as borax, and EDTA sodium salt is also known as sodium edetate, which latter components are recited in Table 2.

Applicant acknowledges with thanks the Examiner's indication that the 103 rejection of claims 41 et al. are likely to be withdrawn in view of the arguments presented at the interview, which arguments are essentially reiterated hereinbelow.

Turning to the Official Action, claims 19-29, 31-34 and 36-38 are rejected under 35 U.S.C. 103 as obvious over Gamache et al. (WO 01/15677) in view of ISTA or Nolan et al.

This ground of rejection is deemed to be overcome by the cancellation of all rejected claims.

Claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60 and 63 are rejected under 35 USC 103 as being unpatentable over Hellberg et al. and Nolan et al. This ground of rejection is respectfully traversed as applied to the pending claims for the reasons explained during the interview.

The Examiner asserts that it would have been obvious to substitute the bifunctional ester compounds of Hellberg et al. having anti-inflammatory and anti-oxidant activity with bromfenac as disclosed in Nolan et al. because of "the art recognized equivalent activity of bromfenac as an

anti-inflammatory agent in topical usage." See Official Action date December 24, 2009 at page 4. Applicant respectfully disagrees that bromfenac is equivalent to the Hellberg bifunctional ester compounds having both anti-inflammatory and anti-oxidant activity.

The intended purpose of the invention disclosed in Hellberg et al. is to provide "[c]ompounds having anti-inflammatory ***and*** antioxidant activity." See Hellberg et al., Abstract (emphasis added); see also Hellberg at column 2, lines 13-18 ("***The present invention provides*** new compounds having potent anti-inflammatory ***and*** anti-oxidant activity.") (emphasis added). Indeed, Hellberg et al. explicitly state that the principle of operation of the anti-inflammatory and antixodixant compounds is to provide a two-pronged therapeutic approach not previously available in the art:

> The compounds of the present invention are capable of protecting against cellular damage by a wide range of insults. Since the compounds provide this protection by decreasing free radical or oxidative damage, reducing cyclooxygenase or lipoxygenase mediated inflammation, and improving site delivery, this therapy represents an improved two-pronged approach to cytoprotection.

See Hellberg et al. at Column 2, lines 57-63. Therefore, the intended purpose of the invention disclosed in Hellberg et al. is to provide compounds with not only anti-inflammatory activity, but also anti-oxidant activity for improved therapeutic functionality:

> The compounds also include an anti-oxidant component. As oxidative stress has been implicated in inflammatory responses, the presence of an anti-oxidant will further help treat the target tissue.

See Hellberg et al. at Column 2, lines 38-40.

Moreover, the compounds of Hellberg et al. are intended to offer advantages not provided by the mere administration of individual agents such as bromfenac. Such intended advantages include a uniform delivery of an active molecule, simplifying issues of drug metabolism, toxicity and delivery, as well as 5-lipooxygenase inhibitory activity not present in the individual agents.

> The use of a single agent having both activities over a combination of two different agents provides uniform delivery of an active molecule, thereby simplifying issues of drug metabolism, toxicity and delivery.

See Hellberg et al. at Column 2, lines 7-10.

> Additionally, the compounds of the present invention exhibit 5-lipoxygenase inhibitory activity not present in the individual compounds.

See Hellberg et al. at Column 2, lines 16-18.

> The compounds of the present invention also exhibit properties present only in the combined molecule, ***not in the individual components***. One such property is the inhibitory efficacy against 5-lipoxygenase, an enzyme known to be involved in inflammation.

See Hellberg et al. at Column 2, lines 41-44 (emphasis added).

An additional intended advantage of the Hellberg bifunctional ester compounds is disclosed at Col. 2, lines 46 to 56:

> Another advantage of the present invention is that the anti-inflammatory moiety and the anit-oxidant moiety are linked through an ester bond. Since the carboxylic acid moiety of the NSAIA has been converted to an ester, the resultant molecule is neutrally charged, thus increasing lipohilicity and drug delivery.

Thus, the Hellberg bifunctional ester compounds are intended to increase lipophilicity and drug delivery relative to bromfenac alone.

The USPTO has made clear that "[i]f [the] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." See MPEP section 2143.01 V, citing *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984). Additionally, section 2143.01 VI of the MPEP plainly states: "The proposed modification cannot change the principle of operation of a reference. If the proposed modification or combination of the prior art would change the principle of

operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." See also *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Here, the proposed substitution of the Hellberg bifunctional anti-inflammatory, anti-oxidant ester compounds with bromfenac would render the Hellberg et al. invention unsatisfactory for its intended purpose of providing "compounds having potent anti-inflammatory and anti-oxidant activity" with increased "lipophilicity and drug delivery" and "5-lipoxygenase inhibitory activity not present in the individual compounds." Applicant respectfully submits that this proposed modification would radically change the principle of operation of Hellberg et al. from "an improved two-pronged approach to cytoprotection" to a mere one-pronged approach based on anti-inflammatory action alone.

Therefore, because bromfenac is not equivalent to the Hellberg bifunctional ester compounds and because the proposed substitution would render the Hellberg et al. invention unsatisfactory for its intended purpose and radically change the principle of operation of Hellberg et al., Applicant respectfully submits a prima facie case of obviousness cannot be based on the combination of Hellberg et al. and Nolan et al.

In addition to the argument that the proposed modification changes the principle operation and intended purpose of Hellberg et al., Applicant submits that Hellberg et al. explicitly teach away from the use of a compound, such as bromfenac, having only anti-inflammatory activity. Hellberg et al. explicitly exclude the use of a single action non-steroidal anti-inflammatory agents such as bromfenac:

> Non-steroidal anti-inflammatory agents (NSAIA) have been used for the treatment of inflammatory disorders. The following references may be referred to for further background concerning this use of NSAIAs:
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> Ophthalmoscope, volume 8, page 257 (1910);
>
> FASEB Journal, volume 1, page 89 (1987); and
>
> Inflammation and Mechanisms and Actions of Traditional Drugs, vol. I Anti-inflammatory and Anti-rheumatic drugs. Boca Raton, Fla., CRC Press, (1985).
>
> However, ***there are some problems associated with NSAIA treatment including delivery to the appropriate site of action and side effects*** (Goodman and Gilman's The Pharmacological

> Basis of Therapeutics, pages 638-669, Pergman Press, NY (1990)).

See Hellberg et al. at Column 1, lines 28-37 (emphasis added).

See also U.S. Patent No. 5,886,030, a copy of which is enclosed, which states:

> Stinging and burning sensations, as well as general discomfort, are often associated with the topical ophthalmic application of certain types of ophthalmic agents. It is believed that such ocular discomfort is due to the presence of certain functional groups in these agents. Examples of such agents which product ocular discomfort include, but are not limited to, β-blockers such as betaxolol; prostaglandins and prostaglandin derivatives; muscarinics such as pilocarpine; a-adrenergics such as epinephrine, clonidine and apraclonidine; cholinergics such as carbochol; and nonsteroidal anti-inflammatory drugs ("NSAIDS") such as diclofenac and suprofen.

See U.S. Patent No. 5,886,030 at Column 1, lines 21-32.

According to the USTPO guidelines, "[i]t is improper to combine references where the references teach away from their combination." See MPEP § 2145, citing *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983); see also *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354 (Fed.Cir. 2001) ("It is well-established that references which "teach away cannot serve to create a prima facie case of obviousness.") (citations omitted).

Here, Hellberg et al. exclude the use of a single NSAIA's by disclosing that such compounds are associated with "problems" such as "side effects" and "delivery to the appropriate site of action." In light of this teaching away from the use of a non-steroidal anti-inflammatory agent (NSAIA), one skilled in the art would not substitute bromfenac, a known NSAIA, for the anti-inflammatory and anti-oxidant compounds disclosed in Hellberg et al. Therefore, because Hellberg et al. teach away from the use of bromfenac, Applicant respectfully submits a prima facie case of obviousness cannot be based on the combination of Hellberg et al. and Nolan et al.

In addition, one skilled in the art would not have been motivated along the lines of the claimed invention by Hellberg et al. The claimed invention uses the second component as a cosolvent to assist in stabilizing the bromfenac. The second component of the claimed invention is an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester, preferably tyloxapol.

Hellberg et al., however, fail to list tyloxapol as a cosolvent. See column 9, lines 1-5. Instead, Hellberg et al. use tyloxapol for an entirely different purpose. Whereas bromfenac is relatively soluble, the bifunctional ester compounds of Hellberg et al. are relatively lipophilic and insoluble. According to Example 3 bridging columns 11-12, the tyloxapol is apparently used as a milling diluent to grind the relatively insoluble bifunctional ester compound of Hellberg et al. to improve the solubility of the more lipophilic Hellberg ester compounds. In addition, the tyloxapol apparently helps to prevent the ground bifunctional ester compounds from aggregating into larger particles. Therefore the only apparent reason that tyloxapol is used in the compositions of Examples 2 and 3 of Hellberg et al. is as a grinding and anti-aggregation agent for the relatively lipophilic insoluble bifunctional ester compounds of Hellberg et al. Hence one skilled in the art, reading Hellberg et al., would not have been motivated to use tyloxapol in combination with bromfenac, because bromfenac does not suffer from the problems of lipophilicity and insolubility relative to the bifunctional ester compounds of Hellberg et al.

For the reasons detailed above, Applicant respectfully requests withdrawal of the rejection of claims 19-38, 41-60 and 63 under 35 USC 103 as being unpatentable over Hellberg et al. and Nolan et al.

Lastly, claims 19-38 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-43 of copending application Serial No. 11/755,662.

It is believed that all other grounds of rejection have been overcome in view of the instant response. Accordingly, it is respectfully submitted that this provisional ground of rejection should be withdrawn and the application passed on to allowance.

In summary, it is believed that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance. Accordingly such allowance is solicited.

Rejoinder and allowance of the withdrawn method claims is also solicited.

Respectfully submitted,

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